

# Combined Thiamidol and Low-fluence Q-switched Nd:YAG Laser for the Treatment of Facial Hyperpigmentation

Vasanop Vachiramon, Kanchana Leerunyakul, Chaninan Kositkuljorn, Pamela Chayavichitsilp  
Division of Dermatology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

## Abstract

**Background:** Thiamidol (isobutylamido thiazolyl resorcinol) is a novel human tyrosinase inhibitor recently shown to be effective in the treatment of hyperpigmentation. Low-fluence Q-switched Nd:YAG 1064-nm laser (LFQS) has proven to be effective for various hyperpigmentary conditions. However, there have been no studies to date on the efficacy and safety of combined Thiamidol and LFQS treatment.

**Objectives:** To compare the efficacy and safety of combined Thiamidol-based serum and LFQS with LFQS monotherapy for facial hyperpigmentation.

**Materials and Methods:** Patients with symmetrical facial hyperpigmentation were treated with five sessions of once weekly LFQS on the whole face. One side was randomly treated with a Thiamidol-based serum formulation and the other side received a placebo cream for 12 weeks. Patients were followed for 8 weeks after the last laser treatment. Relative lightness index (RL\*<sub>I</sub>), Facial Hyperpigmentation Severity Score on the Malar Area (FHSS<sub>m</sub>), patient satisfaction, recurrence, and adverse events were recorded.

**Results:** Twenty-four (N=24) patients completed the study. Both sides demonstrated significant reductions of mean RL\*<sub>I</sub> and mean FHSS<sub>m</sub> from baseline (P < .01). At the 4th week, the Thiamidol-based serum treated side showed more improvement in mean RL\*<sub>I</sub> than the placebo-treated side (62.5% vs 47.3% improvement, P < .05). The mean FHSS<sub>m</sub> on the Thiamidol-based serum treated was reduced at a significantly higher percentage than the placebo-treated side (54.4% vs 40.2% reduction, P < .05). Partial recurrence was observed on both sides. No serious side effects were noted.

**Conclusion:** Combined Thiamidol-based serum and LFQS therapy was superior to LFQS monotherapy in the treatment of facial hyperpigmentation. Thiamidol-based formulations may serve as adjuvant treatment for patients with hyperpigmentation with standard therapy.

## Materials and Methods

### Study Design

This was a prospective, randomized, evaluator-blinded, split-face controlled trial to evaluate the efficacy and safety of combined Thiamidol and LFQS versus LFQS monotherapy in patients with facial hyperpigmentation. Participants were recruited from the outpatient dermatology department of a university-based hospital (Ramathibodi Hospital, Mahidol University, Bangkok, Thailand).

### Compliance with Ethics Guidelines

The study was conducted with approval from the Mahidol University Institutional Review Board for Human Subject Research (Protocol number MURA2019/1064, Thai clinical trial registry number TCTR20200410010). The experimental protocol was approved on October 28, 2019. The protocol of this study complied with the guidelines of the Declaration of Helsinki. Written informed consents were obtained from all participants before enrollment. The patients gave permission for their photographs to be published.

### Patients

Twenty-five patients aged 18 years or above with symmetrical facial hyperpigmentation on both malar areas were included in the study. Patients with hyperpigmentary condition characterized by light to dark brown patches distributed on both sides of the face were recruited. The exclusion criteria were pregnant or lactating women, subjects with a dermatological condition on the treatment area, subjects having used topical or systemic therapy for facial hyperpigmentation within 1 month, and subjects with history of laser therapy within 6 months prior to enrollment.

**REFERENCES:** 1. Wattanakrai P, Mornchan R, Eimpunth S. *Dermatol Surg.* 2010;36(1):76-87. 2. Vachiramon V, Sirithanabadeekul P, Sahawatwong S. *J Eur Acad Dermatol Venereol.* 2015;29(7):1339-1346. 3. Nam JH, Kim HS, Lee GY, et al. *Ann Dermatol.* 2017;29(4):427-432. 4. Kim EH. *Case Rep Dermatol.* 2017;9(2):30-34. 5. Lee Y, Choi EH, Lee SW. *Dermatol Surg.* 2012;38(1):31-37. 6. Seo HM, Choi CW, Kim WS. *Dermatol Surg.* 2015;41(1):142-148. 7. Freitag FM, Cestari TF, Leopoldo LR, et al. *J Eur Acad Dermatol Venereol.* 2008;22(6):655-662. 8. Grimes PE, Ijaz S, Nashawati R, et al. *Int J Womens Dermatol.* 2019;5(1):30-36. 9. Mann T, Gerwat W, Batzler J, et al. *J Invest Dermatol.* 2018;138(7):1601-1608. 10. Prignano F, Ortonne JP, Buggiani G, et al. *Dermatol Clin.* 2007;25(3):337-342. viii. 11. Rivas S, Pandya AG. *Am J Clin Dermatol.* 2013;14(5):359-376. 12. Nordlund JJ, Grimes PE, Ortonne JP. *J Eur Acad Dermatol Venereol.* 2006;20(7):781-787. 13. Arrowitz C, Schoelermann AM, Mann T, et al. *J Invest Dermatol.* 2019;139(8):1691-1698. 14. Shah SD, Aurangabadkar SJ. *J Cutan Aesthet Surg.* 2019;12(2):76-84. 15. Trivedi MK, Yang FC, Cho BK. *Int J Womens Dermatol.* 2017;3(1):11-20. 16. Kim JH, Kim H, Park HC, et al. *J Invest Dermatol.* 2010;130(9):2333-2335. 17. Jones CE, Nouri K. *J Cosmet Dermatol.* 2006;5(1):9-13. 18. Kim JE, Chang CE, Yeo UC, et al. *Clin Exp Dermatol.* 2013;38(2):167-171. 19. Gokalp H, Akkaya AD, Oram Y. *J Cosmet Dermatol.* 2016;15(4):420-426. 20. Ustuner P, Balevi A, Ozdemir M. *J Cosmet Laser Ther.* 2017;19(7):383-390. 21. Laothaworn V, Juntongjinn P. *J Cosmet Laser Ther.* 2018;20(6):320-325. 22. Kwon HH, Choi SC, Jung JY, et al. *J Dermatolog Treat.* 2019;30(4):352-356. 23. Bansal C, Naik H, Kar HK, et al. *J Cutan Aesthet Surg.* 2012;5(4):266-272. 24. Kim JH, Kim DH, Kim JH, et al. *J Cosmet Laser Ther.* 2012;14(6):277-285.

### Treatment

All eligible participants were randomized to apply a Thiamidol-containing serum (Beiersdorf AG, Germany) twice daily on one side of the face for 12 weeks. The contralateral side of the face was assigned to apply placebo cream twice daily for 12 weeks. The Thiamidol-containing product and placebo were prepared and stored in identical bottles, each labeled with a container number and dosing instructions. Laser therapy was performed on the entire face using LFQS (Revlite<sup>®</sup>, Hoya Conbio, Fremont, CA), 6-mm spot size, collimated homogenous flat-top beam profile, to deliver energy at 2.1-2.4 J/cm<sup>2</sup>, 10 Hz for 3 passes until the clinical endpoint of mild erythema was reached. The face was cleansed using a gentle cleanser before each laser treatment. An air cooling device was used during the procedure to relieve pain and protect the epidermis. Compression with ice pack following laser treatment was advised to decrease discomfort. The laser treatment was repeated for a total of 5 sessions at 1-week intervals. After the last treatment, patients were followed up every 4 weeks for 2 visits, for a total of 7 visits. The participants were instructed to apply the Thiamidol serum, placebo cream, and a broad-spectrum sunscreen with sun protection factor of at least 50 beginning on the day of the procedure and avoid sun exposure throughout the study. Topical medications and other whitening products were prohibited during the study period.

### Outcome Evaluation

Standard digital photographs (Visia<sup>®</sup>-CR, Canfield Imaging System, Fairfield, NJ) and colorimeter measurements were obtained at baseline and at every visit. An objective assessment of the treated area was evaluated using a colorimeter (DSM II ColoriMeter<sup>®</sup>, Cortex Technology, Hadsund, Denmark). The lightness index (L\*<sub>I</sub>) was defined as skin lightness on a gray scale ranging from 0 (total black) to 100 (total white). The relative lightness index (RL\*<sub>I</sub>) was calculated from the difference between L\*<sub>I</sub> of the lesion and the surrounding normal skin. The mean RL\*<sub>I</sub> was calculated from the average of measurements on the 3 darkest areas of hyperpigmented patch. Relative lightness index (RL\*<sub>I</sub>) = L\*<sub>I</sub> of normal skin - L\*<sub>I</sub> of hyperpigmented skin. The subjective outcome was assessed by one blinded non-treating dermatologist using digital photographs. The severity of facial hyperpigmentation was evaluated using Facial Hyperpigmentation Severity Score on the Malar Area (FHSS<sub>m</sub>) modified from the Melasma Area and Severity Index (MASI). FHSS<sub>m</sub> was scored based on the following parameters: "A" refers to area of involvement (0-6 points; 0 = 0%, 1 = <10%, 2 = 1%-29%, 3 = 30%-49%, 4 = 50%-69%, 5 = 70%-89%, and 6 = 90%-100%), "D" refers to pigment darkness (0-4 points; 0 = absent, 1 = slightly visible hyperpigmentation, 2 = mild, 3 = marked, and 4 = severe), "H" refers to homogeneity (0-4 points; 0 = minimal, 1 = slight, 2 = mild, 3 = marked, and 4 = severe). The FHSS<sub>m</sub> was calculated based on the three variables: FHSS<sub>m</sub> = (D + H) × A. Patient satisfaction scores were rated by the participants using a visual analog scale (VAS) ranging from 0 (no improvement) to 10 (significant improvement) at the 4th week of treatment and again at the end of the study. Adverse events were assessed and recorded by a physician at every visit.

### Recurrence Evaluation

Recurrence was defined as an increase in RL\*<sub>I</sub> and/or FHSS<sub>m</sub> scores of more than 50% at the end of the study compared with the last day of laser treatment. The recurrence was evaluated at the end of the study. Recurrence rate was calculated as percentage of patients with recurrence as defined above.

### Statistical Analysis

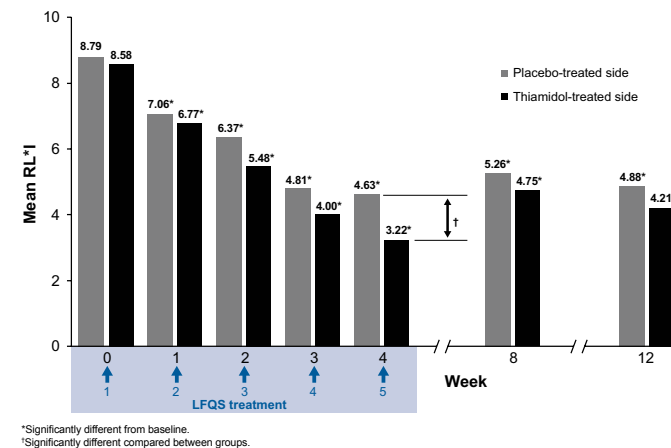
Statistical analyses were performed using STATA/SE version 14.2 (STATA Corp). Categorical variables were expressed as numbers (percentages). Continuous variables were presented as mean ± SD. Multilevel mixed-effects linear regression analysis was used to test continuous variables. A P-value of less than .05 was considered statistically significant.

## Results

**TABLE 1. Patients' demographic data, baseline mean RL\*<sub>I</sub>, and baseline Mean Facial Hyperpigmentation Severity Score on the Malar Area (FHSS<sub>m</sub>).**

Characteristics	N = 24
Mean age (y) ± SD	48.04 ± 7.8
Sex	
Male, n (%)	2 (8.33%)
Female, n (%)	22 (91.67%)
Fitzpatrick skin type	
Type III, n (%)	21 (87.5%)
Type IV, n (%)	3 (12.5%)
Baseline mean RL* <sub>I</sub> ± SD	
Thiamidol-treated side	8.58 ± 3.3
Placebo-treated side	8.79 ± 3.12
Baseline mean FHSS <sub>m</sub> scores ± SD	
Thiamidol-treated side	25.92 ± 9.93
Placebo-treated side	26.42 ± 9.7

**FIGURE 1. Mean Relative Lightness Index (RL\*<sub>I</sub>), LFQS, low-fluence Q-switched Nd:YAG 1064-nm laser.**

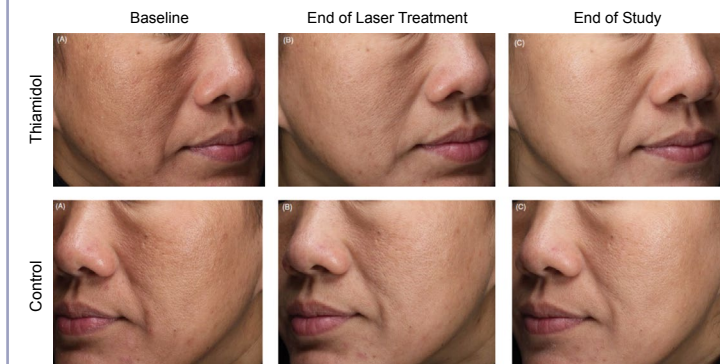


\*Significantly different from baseline.  
†Significantly different compared between groups.

**TABLE 2. Patient satisfaction scores on improvement using visual analog scale (VAS).**

Time	Mean satisfaction score on Thiamidol-treated side (VAS 0-10, n = 24)	Mean satisfaction score on Placebo-treated side (VAS 0-10, n = 24)	P-value
Week 4 (End of laser treatment)	6.87 ± 2.37	6.65 ± 2.39	0.329
Week 12 (End of the study)	7.26 ± 2.62	7.08 ± 2.46	0.583

**FIGURE 2. Reduction of Hyperpigmentation by combined laser and Thiamidol treatment.** Photographs of representative subjects from Thiamidol and control group. **A.** Baseline; **B.** End of Laser Treatment; **C.** End of Study.



## Summary and Conclusions

- This is the first randomized, prospective study using combined Thiamidol and LFQS in the treatment of facial hyperpigmentation
- This study shows that combining Thiamidol with LFQS results in greater reduction and faster clinical improvement of hyperpigmentation than LFQS monotherapy
- Recently, Thiamidol (isobutylamido thiazolyl resorcinol) has been identified as an effective inhibitor of human tyrosinase
- From these results, Thiamidol may serve as a safe and effective adjunctive treatment option for patients with hyperpigmentation